Chronic Kidney Disease: An Inherent Risk Factor for Acute Kidney Injury?

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Epidemiologic evidence suggests that chronic kidney disease (CKD) is a risk factor for acute kidney injury (AKI) due to the prevalence of CKD in patients who have episodes of AKI. However, the high burden of comorbidities such as age, diabetes, peripheral vascular, cardiovascular, and liver disease accompanying CKD, and the difficulties of defining AKI in the setting of CKD make these observations difficult to interpret. These comorbidities not only could alter the course of AKI but also may be the driving force behind the epidemiologic association between CKD and AKI because of systemic changes and/or increased exposure to potential nephrotoxic risks. Here, we contend that studies suggesting that CKD is a risk factor for AKI may suffer from residual confounding and reflect an overall susceptibility to illness rather than biologic susceptibility of the kidney parenchyma to injury. In support of our argument, we discuss the clinical evidence from epidemiologic studies, and the knowledge obtained from animal models on the pathophysiology of AKI and CKD, demonstrating a preconditioning influence of the previously impaired kidneys against subsequent injury. We conclude that, under careful analysis, factors apart from the inherent pathophysiology of the diseased kidney may be responsible for the increased frequency of AKI in CKD patients, and the impact of CKD on the risk and severity of AKI needs further investigation. Moreover, certain elements in the pathophysiology of a previously injured kidney may, surprisingly, bear out to be protective against AKI.

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With the coining of the term "risk factor" by the original Framingham study investigators, the search for identifiable risk factors for chronic diseases has grown exponentially, and the population science of risk factor analysis (1) has burgeoned. A risk factor, strictly defined, is a measurable or observable trait that can be detected before development of an outcome of interest and is associated with the outcome independent of other measurable traits. Typically, a risk factor includes both causal and predictive factors. While not always in the causal pathway, the potential value of a risk factor is increased by biologic evidence of causality. In fact, the utility of a risk factor is dependent on a number of other issues, such as whether it is modifiable, whether it is easily separated from the outcome of interest, and finally, whether it predisposes to an increased frequency and/or severity of the outcome.

Chronic kidney disease (CKD) is commonly labeled as a risk factor for acute kidney injury (AKI) because of the epidemiologic association between the two (2,3), and it is accepted as such without much contention. The underlying reasons for this association have not been given much attention, perhaps because of an assumed biologic plausibility of a diseased kidney being more vulnerable to further injury. We discuss here some of the complicating factors, both epidemiologic and biologic, in considering the evidence for this association specifically as it relates to the frequency and severity of AKI in pre-existing kidney disease. We first review the available epidemiologic evidence, and then the basic science observations, which call into question the assumption that the diseased kidney itself is more vulnerable to injury.

Influence of CKD on AKI

A number of studies in various settings (4–10) have reported an association between pre-existing CKD and AKI. The first consideration in examining the influence of pre-existing CKD on the increased likelihood of AKI is whether these observed associations are largely confounded by the comorbidities associated with CKD, altered by repeated exposure to various nephrotoxic insults or in-hospital errors (11,12), or primarily due to the altered physiology in CKD. These factors are not necessarily exclusive, as the comorbidities *per se* may lead to more frequent exposure to nephrotoxic insults and/or alter the response to an acute insult. For instance, high cardiovascular disease incidence in CKD with exposure to contrast agents, use of ace inhibitors or angiotensin receptor blockers in the presence of undiagnosed renal artery stenosis, or impaired autoregulation of renal blood flow in patients with diabetes permitting low renal perfusion during systemic hypotension can all lead to increased susceptibility to AKI. Although this suggests that CKD patients are more likely to be exposed to various potentially nephrotoxic insults than the general population, it need not imply an in-

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creased vulnerability of the diseased kidney to incur injury during a particular insult.

CKD has been identified as a risk factor for AKI after multivariate adjustment for comorbidities in the settings of radiocontrast administration, sepsis, and cardiac surgery (4). Statistical adjustments for comorbidities are not uniform among various studies, nor are entirely adequate, despite advanced methods such as propensity scoring to capture the residual confounding by the greater overall illness burden in CKD patients. Clinical studies typically capture the outcome of AKI and determine the presence of CKD in the denominator. This does not allow the discrimination between the above discussed factors that may contribute to the increased risk. A better method to determine the true risk of AKI in patients with CKD would be to capture the incidence of single or repeated AKI episodes during the natural history of CKD and whether the association persists after adjusting for the increased frequency of medical illness and hospitalization in this population. Prospectively designed studies such as the ongoing Chronic Renal Insufficiency Cohort (CRIC) study should shed some light on the frequency of AKI events in a CKD population.

Other methodological issues such as how CKD and AKI are defined in clinical studies may further affect the validity of observed associations. The definition for CKD is not uniform among different studies and very few studies use valid measurements to assess baseline kidney function. Frequently, a preoperative creatinine value is used as a marker of pre-existing renal insufficiency, which may not truly reflect the diagnosis of CKD. Definitions of AKI in the published literature range from a 0.3 mg/dl rise in serum creatinine to need for dialysis. The use of an absolute increase in creatinine, a percentage decrease in estimated GFR (eGFR), or an in-hospital value to define CKD introduces a bias toward detection of AKI in patients with CKD in observational studies. The recently introduced definitions of AKI, RIFLE (Risk-Injury-Failure-Loss-End stage kidney disease), or AKI Network criteria also use a percentage decrease in eGFR or an absolute increase in creatinine, respectively. Waikar and Bonventre have highlighted the substantially different effects of these definitions at different levels of kidney function by creatinine kinetics simulation (13).

Hsu *et al*. recently described the risk of severe AKI requiring renal replacement in hospitalized patients with CKD compared with a control non-CKD population (14). Besides CKD, comorbidities such as diabetes, hypertension, and proteinuria at baseline were found to be independent risk factors for AKI. Adjusting for some of the confounding variables decreased the odds between baseline CKD and AKI, but the overall association was maintained. AKI was defined as dialysis-requiring acute renal failure in the study. Because the clinical decision to dialyze a patient is frequently influenced by a higher overall serum creatinine, presence of hemodialysis access, or consideration of inevitable progression to ESRD, this definition of AKI could bias toward capturing more AKI cases in CKD patients. Moreover, in patients with advanced CKD, the progression of CKD to ESRD may sometimes be difficult to separate from acute-on-chronic renal failure.

The second consideration is whether pre-existing CKD conditions the outcome of AKI. To carefully answer this question, determination of severity of injury in patients with or without CKD exposed to similar kinds of insults may be required, as it is difficult to separate the contribution of the insult leading to AKI from that due to the presence of CKD. Using serum creatinine as both the exposure and outcome variable limits the ability to differentiate acute from chronic kidney disease and makes the analysis of interactions between AKI and CKD difficult. Necessity of dialysis as a marker of severity of AKI is again problematic when considered in the context of acute-on-chronic renal failure as discussed above. Currently, there is no single biomarker that can differentiate acute from chronic kidney disease, which can help to address this issue.

Unequivocal clinical evidence to support increased severity of AKI in CKD patients is certainly lacking. Wald *et al*. assessed the future implications of in-hospital AKI requiring dialysis and found more frequent episodes of AKI and higher absolute risk for ESRD after AKI in patients with CKD (defined by diagnostic codes). However, the relative risk of ESRD after an episode of AKI was greater in those without CKD *versus* those with CKD. This may suggest a greater severity of AKI in those without pre-existing CKD, but may also be reflective of greater specificity of administrative codes for AKI among those without CKD or be driven by the very low number of ESRD cases in patients without documented AKI or CKD in the study (15). In-hospital mortality, while obviously affected by intercurrent illness, is frequently considered a surrogate for the severity of AKI. Several large observational and database studies report, surprisingly, lower in-hospital mortality in patients with AKI superimposed on CKD compared with controls (16–19,4,20,21). Recent data from the Program to Improve Care in Acute Renal Disease again reveals lower in-patient mortality and median ICU length of stay in patients with acute-on-chronic renal injury compared with non-CKD patients with AKI, though the postdischarge dialysis rates were higher in patients with pre-existing CKD (22).

Evidence from the Laboratory: Biologic Plausibility

We now turn to the available experimental data on the pathogenesis of AKI and pathophysiology of CKD to assess the biologic susceptibility of the diseased kidney parenchyma to subsequent injury.

Pathogenesis of AKI

The early impressions from animal data suggested that AKI was principally a "vasomotor nephropathy" because renal vasoconstriction was a prominent feature in various forms of AKI (23,24). The vasoconstriction was thought to be the result of activation of tubuloglomerular feedback (TGF), as tubular injury from AKI resulted in impaired proximal reabsorption, which led to increased salt delivery to macula densa, thus activating TGF. Enhanced responses to vasoconstrictor stimuli and decreased vasodilatory responses were also observed (25). These hypotheses were strengthened by the observations that volume depletion worsened, whereas high salt intake and a hyper- or euvolemic state ameliorated the severity and mortal-

ity rate in AKI (26,27). Importantly, the hemodynamic basis of AKI was also demonstrated in human studies in various settings (28–30,24,31). Subsequent studies raised questions about the universality of the "vasomotor nephropathy" hypothesis, with reduction in glomerular ultrafiltration coefficient, tubular backleak of solutes, and tubular obstruction demonstrated as additional mechanisms reducing GFR (32,33). In ischemia-reperfusion, the most commonly utilized animal model of AKI, the role of reactive oxygen species and oxidant stress via various inflammatory mediators has been delineated in sublethal and lethal tubular cell injury. On the basis of our current understanding, various hemodynamic and cellular mechanisms known to condition the response to ischemic AKI are enumerated in Table 1.

Pathophysiology of CKD

The assumed biologic plausibility of a diseased kidney vulnerable to subsequent injury arises from the notion that various diseases lead to disordered, progressive deterioration in structure and function of all or most nephrons in the kidney. Surely, in such a chaotic environment, another insult would result in significant injury because of the impaired functional capacity of the surviving nephrons. However, established knowledge based on physiological data from 4 decades ago illustrates the striking homogeneity of function and regulatory capacity in the surviving nephrons despite the extensive renal parenchymal damage in kidney disease. This theory known as the "intact nephron" hypothesis was first elegantly described and discussed along with the supporting data in 1960 and has been revisited more recently (34–36). The diseased kidney responds in a predictable and organized manner to the changing needs of the body by invoking adaptations in glomerular and tubular function in the surviving nephrons to maintain homeostasis. This is evident by uniformity of glomerulotubular balance, tubular transport adaptations such as increased potassium secretion and decreased phosphate reabsorption, and hyperfiltration in the residual nephrons until late stages of the disease.

So the decline in renal reserve in CKD, which is frequently the basis for considering CKD a risk factor for AKI, really refers to fewer, but functionally intact, nephrons. Moreover, low functional reserve alone, independent of other comorbidities, should not necessarily have any bearing on the probability of incurring an acute insult and does not explain the increased likelihood of AKI implied by the epidemiological data. The reduction in functioning nephrons could impart a risk of more severe injury once an insult occurs, but this is not borne out in animal or human studies.

Clinical abnormalities in CKD are influenced by the rapidity and the extent of nephron obliteration, independent of the specific etiology. Consequently, the pathophysiology of the kidney disease truly relates to the behavior of the surviving nephrons as they maintain renal function under ongoing stress. This behavior has been classically studied in the subtotal nephrectomy (STN) or the 5/6th nephrectomy model of progressive renal dysfunction due to severe nephron mass reduction. Although STN does not mimic certain phenotypical and causal elements of human disease, it has been a valuable model to reproduce the consequences of reduced functional renal mass that are observed in practically all forms of CKD. It is characterized initially by compensatory kidney growth and hyperfiltration with an elevated glomerular capillary pressure, followed eventually by the development of progressive glomerulosclerosis and interstitial disease. There are several important differences between CKD experienced by patients and the animal models to study them, perhaps the most important being the various comorbidities such as diabetes and atherosclerotic disease that accompany human CKD, not replicated in animal models. But these animal models also allow us to study inherent pathophysiology of CKD and its effect on AKI separate from the influence of comorbidities.

Several metabolic alterations have also been observed in STN. Studies by Harris and Nath have demonstrated increased oxidant stress and high oxygen consumption when factored by sodium reabsorption in STN (37,38). We have also verified the major increase in renal oxygen consumption and noted low functional nitric oxide (NO) activity (39), and a variety of molecular changes such as increased NADPH oxidase expression and ERK phosphorylation early after STN. Baylis and co-workers have also noted low NO activity with reductions

Table 1. Factors influencing the outcome in ischemic AKI

Worsening Factors	Ameliorating Factors
Increased ANG II activity[a]	Blockade of ANG II activity
Reduced nitric oxide activity, particularly endothelial and neuronal nitricoxide synthase[a]	Increased nitric oxide activity
Volume depletion	Volume expansion/high salt intake
Reduced osmolar clearance per nephron	Increased osmolar clearance per nephron[a]
Increased oxygen requirements[a]	Decreased oxygen consumption/demand
Deficient antioxidant systems	Enhanced antioxidant systems[a]
Responsive TGF system	Suppression of TGF[a]
Reduced nephron blood/plasma flow[a]	

[a]Refers to factors that have been observed in experimental models of CKD that may ameliorate or worsen the response to ischemic AKI.

in nitric oxide synthase-1 (NOS-1) expression and increased levels of ADMA, a naturally occurring inhibitor of NOS in STN (40). Several of these alterations to the metabolic and hormonal milieu of the kidney could increase the susceptibility to injury in AKI (Table 1).

Nonetheless, increased single-nephron GFR (SNGFR) or hyperfiltration in the residual nephrons is among the various adaptations early in STN to counteract ongoing and progressive nephron loss. The mechanisms that allow the nephron to hyperfilter must override the constraints that normally prevent SNGFR from rising. It is likely that while doing so, the mechanisms preserving overall GFR may also precondition the kidney to withstand further injury and prevent the fall in GFR when faced with an acute insult. The prototype for such a mechanism is TGF, which interacts with glomerulotubular balance to stabilize the SNGFR. A detailed discussion on the relationship between glomerulotubular balance and TGF has recently been published (41). Any primary increase in SNGFR or a reduction in proximal tubular reabsorption will increase the flow to macula densa and activate TGF, which will in turn constrain SNGFR. Hence, for hyperfiltration to endure, some alteration of the TGF system becomes necessary. When we examined TGF activity at early stages after STN in rats, no TGF response was observed (42). Furthermore, *paradoxical* restoration of TGF response in STN was observed with angiotensin II blockade, as typically, TGF response is subdued by blocking angiotensin II. This anomalous TGF activity, regardless of the exact underlying mechanisms, could influence the susceptibility to AKI, as TGF when activated because of decreased reabsorption by the injured proximal tubule in AKI reduces the SNGFR (*vide supra*).

Our preliminary data demonstrate a resistance in the STN kidney to injury when exposed to an acute ischemic insult, with a relatively preserved GFR and histology compared with controls (43). Treatment of STN animals with angiotensin II blockade led to a greater reduction in GFR after ischemia, presumably because of the restoration of TGF in STN. Although these preliminary results imply a degree of protection imparted by the diseased kidney against a subsequent injury, the model of a single ischemic insult by complete cessation of blood flow does not duplicate the clinical reality of human AKI where patients are frequently exposed to a combination of insults that sometimes recur during a single episode of AKI.

Nevertheless, a modification in the pre-existing environment in the kidney can alter the responses to the mediators of injury in AKI. There is extensive literature that demonstrates that preceding injury of a similar or dissimilar nature confers protection against subsequent insults in the kidney (44,45). Vercauteren and Zager have found lesser degrees of functional and histologic impairment after varying degrees of ischemia in STN animals compared with controls (46,47). Others have found less nephrotoxicity from uranium during second exposure to the agent and in animals with a previous renal injury such as nephritis. Similar findings were observed on repeated exposure to glycerol and protection against mercuric chloride in animals with prior glycerol nephrotoxicity (48,49). This form of "preconditioning" has been observed in other organs as well, particularly in response to recurring ischemic insults (44,23).

Several pathways may contribute to this preconditioning by previously injured kidneys. One such recently studied pathway may be through the activation of hypoxia inducible factor (HIF), a transcriptional complex that oversees the expression of a variety of hypoxia responsive genes and is a master regulator of hypoxia response. As discussed above, in early stages of STN, increased oxygen consumption for transport and other cellular processes can lead to a hypoxic intrarenal microenvironment. There is some evidence for tubular hypoxia and upregulation of HIF in the early stages of STN (50). In conditions of experimental hypoxia, upregulation of HIF has been demonstrated in the proximal tubular cells (50,51). The HIF target proteins have important functions in renal hemodynamics (nitric oxide synthase-2 and heme-oxygenase-1), energy metabolism (glucose transporters and glycolytic enzymes), angiogenesis (VEGF), and cell proliferation/survival (ERK activation) (52). Many molecules and signaling pathways important for preconditioning in kidneys and other organs have been linked back to HIF (53–57). HIF activation is increasingly being recognized as a protective measure against AKI in normal kidneys (52,58–62). The underlying mechanisms offering this protection have not been extensively explored, but enhanced antioxidant systems such as heme-oxygenase, inducing glycolytic capacity in proximal tubular cells, normally incapable of glycolysis, inhibition of oxidative metabolism, or inducing proliferating cells may all be potential mechanisms (44,63–65).

Conclusion

There is increased recognition of and interest in the relationship between AKI and CKD. Clinical observations suggest that AKI occurs frequently in the presence of CKD. However, various confounders make it difficult to assess CKD as an independent risk factor. Known comorbidities that are both causes and consequences of CKD, the concurrent increase in procedures and medical therapies constituting potential causes of AKI, and issues of definition of both predictor and outcome may influence this risk. Preclinical data demonstrate that various adaptations in (patho)physiology of CKD can alter the response to AKI, and a protective preconditioning influence of a prior injury on subsequent injury in the kidney has been frequently observed. Hence, the generally accepted notion that CKD is a causative risk factor for AKI merits further examination and analysis. The hemodynamic and molecular preconditioning pathways, once clearly elucidated by further research, can be manipulated artificially as potential preventive and therapeutic measures in CKD and AKI.

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Disclosures

None.

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